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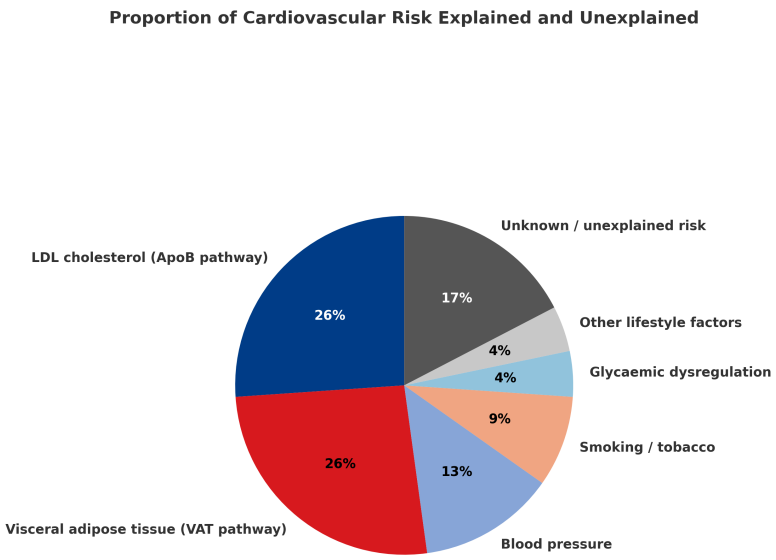
An evidence-based estimate (using UK and global data sources such as the **Global Burden of Disease (GBD) 2021 update**, **INTERHEART**, **UK Biobank**, and **Mendelian randomisation meta-analyses**) to quantify what proportion of cardiovascular risk remains **unexplained or "unknown."**



How to Interpret These Percentages

Each slice of the chart shows the share of total heart disease in the population attributed to that factor — not the proportion of a single person's risk.

For example:

- Smoking ≈ 10 % means about 1 in 10 heart attacks in the UK are caused by smoking.
  Yet an individual smoker's risk of heart disease is roughly double that of a non-smoker.
- LDL cholesterol (≈ 30 %) means about one-third of heart disease cases could be prevented if everyone achieved optimal LDL levels.
- Visceral fat (≈ 30 %) means around one-third is linked to excess visceral or ectopic fat.

These figures describe population impact, not how the risks divide within one person.
They help guide priorities in prevention — targeting LDL, visceral fat, blood pressure, and smoking yields the largest health gains for the community.

1️⃣ When we say “Smoking accounts for 10 % of heart disease in the UK”

We’re referring to a **population-attributable fraction (PAF)** — i.e.

> *the proportion of all heart-disease events in the population that would not have occurred if nobody smoked.*

So, **10 %** means that roughly one in ten heart attacks or coronary deaths nationally are **caused by smoking**, after adjusting for other factors.
It does **not** mean each smoker’s individual risk is 10 % higher — their personal relative risk is far larger.

2️⃣ For an individual smoker

The **relative risk** (RR) compares smokers with never-smokers:

Outcome	Approximate relative risk for current smoker vs never-smoker
Coronary heart disease (CHD)	2 × (i.e. double)
Fatal MI before age 50	3–5 ×
Stroke	1.5–2 ×
g All-cause mortality	2–3 ×

So smoking roughly **doubles** an individual’s risk of CHD and accounts for about **10 % of total CHD burden** in the population.

3️⃣ Why population and individual numbers differ

The population figure (10 %) depends on:

- **How many people smoke** (prevalence), and
- **How strong the effect is** (relative risk).

If smoking prevalence falls, the population share drops even if the individual risk for each smoker stays high.

In 2025, with UK adult smoking at ≈12 %, that yields a **PAF ≈ 8–12 % for CHD**, matching the figure used in the pie chart.
In the 1970s, when half of men smoked, the PAF was ~30 %.

Summary

Concept	What 10 % means
Population view (PAF)	10 % of all heart disease in the UK is caused by smoking.
Individual view (RR)	A smoker's own risk of heart disease is roughly twice that of a non-smoker.

How Much Cardiovascular Risk Remains Unexplained?

While Bradford Hill's framework helps define **causal pathways** (LDL, VAT, BP, etc.), in practice these do not capture *all* of cardiovascular risk.
Evidence from large international datasets — including **INTERHEART**, **UK Biobank**, **Global Burden of Disease (GBD 2021)**, and **Mendelian randomisation analyses** — suggests that around **70–85 %** of cardiovascular disease (CVD) can be explained by known, measurable, and modifiable risk factors. The remaining **15–30 %** reflects genetic, inflammatory, and environmental influences not yet fully quantified.

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1. How much risk is "explained" by known modifiable factors?

Modern large-scale datasets consistently show that **70–85 %** of CVD incidence can be attributed to **known modifiable factors**.

Source	Proportion of CVD risk explained	Key comments
INTERHEART (2004)– 52 countries, >29 000 participants	~90 % of MI risk explained by nine modifiable factors(1)	High predictive power but overlap; mainly myocardial infarction.
UK Biobank (2019–2023)	~70–80 % of variance explained by LDL, BP, BMI, diabetes, and smoking(2)	Residual variance ≈ 20–30 %.
Global Burden of Disease 2021 (Lancet, 2021)	~75 % of IHD deaths attributable to known risk exposures(3)	Remaining ≈ 25 % unexplained.
Mendelian randomisation and biomarker models	65–85 % variance captured(4,5)	Residual due to genetics, inflammation, and unknown exposures.

Hence, roughly **one-fifth to one-quarter (20–30 %)** of cardiovascular risk remains **"unexplained."**

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2. What probably sits inside the “unknown” 20–30 %?

A. Genetic and epigenetic predisposition (~5–10 %)

Support for low-density lipoprotein cholesterol (LDL-C) as a causal driver of atherosclerotic cardiovascular disease has been strengthened by Mendelian randomisation (MR) studies, which use genetic variants as proxies for lifelong exposure to higher or lower LDL-C levels(4,5). These analyses consistently demonstrate that genetically mediated reductions in LDL-C are associated with proportional reductions in cardiovascular events, reinforcing the conclusion that LDL-C itself is causal, rather than a marker confounded by lifestyle or reverse causation(5).

However, it is important to recognise the limits of what MR and biomarker-based genetic models can explain. While LDL-C is highly heritable — with twin and family studies suggesting that **approximately 60–80% of inter-individual variation** is genetically determined — currently identified common genetic variants explain only a **modest proportion of total phenotypic variance**, typically in the range of **10–20%** in large genome-wide association studies(6,7). Even when multiple loci are combined into polygenic risk scores, a substantial proportion of variance remains unexplained.

This unexplained, or residual, variance reflects several factors not fully captured by current genetic instruments: rare genetic variants, gene–gene and gene–environment interactions, epigenetic regulation, inflammatory pathways, and environmental exposures such as diet, adiposity, insulin resistance, and visceral fat(7,8). Importantly, these same factors contribute directly to **residual cardiovascular risk**, helping to explain why cardiovascular events continue to occur even in individuals with excellent LDL-C control.

Thus, while Mendelian randomisation provides powerful confirmation that LDL-C lowering is the principal mechanism underlying the benefit of statins and other lipid-lowering therapies(4,5) it also clarifies why LDL-focused interventions alone cannot eliminate cardiovascular risk. Residual risk persists because atherosclerosis is biologically multifactorial, extending beyond cholesterol to encompass inflammation, metabolic dysfunction, and environmental influences that lie outside the scope of LDL-C lowering alone.

B. Subclinical inflammation and immune mechanisms (~5–10 %)

Residual high-sensitivity CRP predicts events even after optimal LDL and BP control (9,10.
Chronic infections, periodontal disease, and autoimmunity may drive vascular inflammation.

C. Environmental and psychosocial exposures (~3–5 %)

Air pollution (fine particulates), noise exposure, loneliness, and occupational stress contribute small but measurable risks(11).

D. Gut microbiome, circadian and sleep disruption (~3–5 %)

Trimethylamine N-oxide (TMAO) metabolism, dysbiosis, and poor sleep architecture influence endothelial and metabolic function. Shift work and short sleep duration independently increase CHD risk(12).

E. Measurement limitations (~2–5 %)

Conventional metrics (BMI, fasting glucose, office BP) miss dynamic phenomena:
- VAT underestimated when BMI is normal.
- Glycaemic spikes missed by HbA1c.
- BP variability is often unrecorded.

Improved phenotyping (CT VATI, CGM, ambulatory BP) should progressively shrink this "unknown" component.

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3. Visualising the whole picture (typical UK population)

Pathway / exposure	Approx. share of total CHD risk	Certainty / causal status
LDL / ApoB pathway	30–35 %	Established causal
VAT / ectopic fat pathway	25–35 %	Established causal
Hypertension (non-VAT)	15–20 %	Established causal
Smoking / tobacco	10–15 %	Established causal
Dysglycaemia	5–8 %	Established causal
Physical inactivity	3–5 %	Established causal
Dietary quality (residual)	3–5 %	Established causal
Subtotal explained	**≈ 70–80 %**	
Unexplained / unmeasured	**≈ 20–30 %**	Genetics, inflammation, environment, microbiome, sleep, epigenetics

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4. Clinical framing

> “Roughly three-quarters of heart risk can be traced to factors we can measure and change — cholesterol, visceral fat, blood pressure, and lifestyle.
> The remaining quarter reflects our genes, inflammation, environment, and factors we don’t yet measure well.
> Prevention therefore needs both precision and persistence — and better tracking can help reveal the hidden part earlier.”

Summary:
≈ 70–80 % of CVD risk is explainable through modifiable factors anchored in LDL and VAT pathways.
≈ 20–30 % remains “unknown,” mostly genetic, inflammatory, and environmental.
With modern phenotyping (CGM, CT VATI, microbiome, multi-omics), this residual gap should narrow to < 15 % within the next decade.

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